STUDIES ON THE MECHANISM OF ALKYLATION BY MANNICH BASES OF THE INDOLE SERIES

BY

ERNEST LUDWIG ELIEL

D.C.F.Q., University of Havana, 1946

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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Introduction

There are two mechanisms by way of which alkylations with Mannich bases (1,2,3), may be supposed to proceed: either through a direct substitution of the amine residue by the compound which is alkylated, or through an elimination of the amine followed by a Michael addition as proposed by Robinson (4) and by Mannich (5).

Either of these mechanisms can be written for alkylations with gramine (3-dimethylaminomethylindole), a Mannich base of indole.

In order to test whether the possibility of amine elimination is a requisite for alkylation, it seemed desirable to investigate the synthesis and alkylating properties of a Mannich base of a 1-alkylindole. Such a compound is not capable of amine elimination, and if it acts as an alkylating agent, it must do so by a direct substitution mechanism.

Discussion Of Results

1-Methyl-3-dimethylaminomethylindole (1-methylgramine) was readily obtained from 1-methylindole, dimethylamine and formaldehyde in aqueous acetic acid solution. Treatment of the base with methyl iodide in alcoholic solution gave the methiodide in nearly quantitative yield.

1-Methylgramine methiodide proved to be an active alkylating agent, being in this respect similar to gramine methiodide and superior to benzyltrimethylammonium iodide. It reacted with aqueous sodium cyanide to yield a mixture of 1-methylindole-3-acetonitrile and 1,3-dimethyl-2-cyanoindole. The structure of the substituted acetonitrile was proved by hydrolysis to 1-methylindole-3-acetic acid, followed by de-

carboxylation to 1,3-dimethylindole, and by reduction to 1-methyltryptamine. The structure of the cyanoindole was proved by hydrolysis to the corresponding amide and acid which were synthesized by an unequivocal path. The allylic rearrangement observed in this reaction resembles that occurring in the reaction of furfuryl chloride with cyanides (6,7).

1-Methylgramine methiodide reacted with acetamidocyanoacetic ester to yield an alkylation product the saponification of which gave rise to a mixture of 1-methyltryptophan and N-acetyl-1-methyltryptophan. The melting point of the amino acid did not agree with that recorded in the literature (8) but its structure was established definitely by decarboxylation to 1-methyltryptamine.

The reaction of 1-methylgramine with the sodium salts of malonic ester, cyanoacetic ester, cyanomalonic ester and tricarbethoxymethane gave rise to alkylation products which were hydrolyzed to (1-methyl)skatylmalonic acid. The structure of the latter was proved by decarboxylation to 1-methylindole-3(β)-propionic acid which was converted to 1-methyltryptamine by a Curtius degradation.

1-Methylgramine reacted with aqueous alkali to yield 1,1′-dimethyl-3-3′-diindolylmethane whose structure was demonstrated by an unequivocal synthesis.

The amine exchange of 1-methylgramine methiodide with piperidine gave rise to 3-piperidinomethyl-1-methylindole which was also obtained by a Mannich reaction from 1-methylindole.

1-Methylgramine methiodide entered into reaction with the methyl and phenyl Grignard reagents to yield 1-methyl-3-ethylindole and 1-methyl-3-benzylindole respectively. The structure of the 3-ethyl compound was proved by independent synthesis. Gramine methiodide reacted with the methyl and phenyl Grignard reagents, the products being 3-ethylindole

and 3-benzylindole respectively. A by-product in this reaction had the composition and properties of *sym.*-3,3′-diindolylethane.

These reactions of 1-methylgramine methiodide constitute facile syntheses of the otherwise inaccessible 3-substituted 1-alkylindoles.

1-Methylgramine alkylated acetamidomalonic ester, cyanoacetic ester and tricarbethoxymethane. The alkylation products were saponified and the resulting acids were identified with the corresponding products obtained from 1-methylgramine methiodide. The alkylation reactions with 1-methylgramine proceeded in the absence of a catalyst. The reaction temperature was substantially higher than in corresponding alkylations with gramine.

1-Methylgramine did not undergo amine exchange with piperidine in refluxing hexanol, but the exchange took place when boron fluoride was added as a catalyst or when 1-methylgramine hydrochloride was substituted for the free base. It is concluded that the amine exchange reaction is acid-catalyzed.

Acid catalysis has also been demonstrated in the case of the self-alkylation of 1-methylgramine to 1,1′-dimethyl-3,3′-diindolylmethane. This reaction did not proceed in boiling aqueous alcohol in the presence of sodium acetate, or at 225° in the presence of sodium methoxide and metallic sodium, but it proceeded readily in refluxing aqueous acetic acid.

For purposes of comparison, a few reactions of benzyldimethylamine have been studied. This amine reacted with tricarbethoxymethane to yield a mixture of benzylmalonic and dibenzylmalonic esters. These esters were identified by hydrolysis to the corresponding malonic acids followed by decarboxylation to hydrocinnamic and dibenzylacetic acids.

From the experimental evidence the conclusions are reached that alkylations by Mannich bases may proceed by a mechanism of direct substitution and that the reaction is

acid-catalyzed.

BIBLIOGRAPHY

(1) Blicke in "Organic Reactions", Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 303.

(2) Snyder, Abstracts of the Tenth National Organic Chemistry Symposium of the American Chemical Society, Boston 1947, p. 31.

(3) Brewster, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1948.

(4) DuFeu, McQuillin and Robinson, J. Chem. Soc., 1937, 53.

(5) Mannich, Koch and Borkowsky, Ber., 70, 355 (1937).

(6) Runde, Scott and Johnson, J. Am. Chem. Soc., 52, 1284 (1930).

(7) Reichstein, Ber., 63, 749 (1930).

(8) Wieland, Konz and Mittasch, Ann., 513, 1 (1934).

VITA

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